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FORM 1 SPRUSON & FERGUSON

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COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

Thomas Julius Borody, of 144 Great North Road, Five Dock, New South Wales, 2046, AUSTRALIA; David A Cooper, of 77 O'Sullivan Road, Rose Bay, New South Wales, 2029, AUSTRALIA, hereby apply for the grant of a standard patent for an invention entitled:

Oral Antibody Therapy For Patients With Lowered Immune Response And Composition Therefor

which is described in the accompanying provisional specification.

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DATED this FOURTH day of AUGUST 1988

Thomas Julius Borody, David A Cooper

By: A G Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
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ORAL ANTIBODY THERAPY FOR PATIENTS WITH LOWERED IMMUNE RESPONSE AND COMPOSITION THEREFOR

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(57) Claim

1. A method for the curative and/or prophylactic treatment of enteric infections/infestations in patients suffering from conditions wherein a lowered immune response is manifested, said method comprising administering to said patient milk, a fraction thereof or milk product produced by a non-human, milk producing animal or antibody product derived therefrom, wherein the animal has been immunologically challenged, to give an immune response, with one or more immunogens relevant to the enteric infection/infestation.

4. The method of Claim 1 wherein said immunogen is selected from the following microorganisms:

a) Cryptosporidium enteritides,
b) Isoporo belli,
c) Giardia,
d) Cytomegalovirus,
e) Salmonella,
f) Shigelli,
g) Candida,
h) Rotavirus,
i) Blastocystis hominis,
j) Herpes virus simplex,
k) Entero-toxogenic E. coli,
l) Aeromonas,

m) Mycobacterium Avium intracellulare,
n) Yersinia entero-colitica,
o) Toxoplasma gondii,
p) Clostridium difficile,
q) Campylobacter jejuni/coli,
r) Entamoeba histolytica, and
s) HIV virus.

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FORM 10

COMMONWEALTH OF AUSTRALIA

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COMPLETE SPECIFICATION

(ORIGINAL)

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Complete Specification for the invention entitled:

Oral Antibody Therapy For Patients With Lowered Immune Response And Composition Therefor

The following statement is a full description of this invention, including the best method of performing it known to me/us
5815/2

ORAL ANTIBODY THERAPY FOR PATIENTS WITH LOWERED IMMUNE RESPONSE AND COMPOSITION THEREFOR

Technical Field

The invention relates to a method of treatment or prophylaxis of enteric infections/infestations in patients with lowered immune response, in particular to the treatment of AIDS patients, and to pharmaceutical compositions useful in this method.

Background Art

Patients in the advanced stages of AIDS frequently suffer with diarrhoea, malabsorption and progressive weight loss. These conditions may be contributed to in part by enteric and colonic infections but also by an AIDS enteropathy. In view of the AIDS patients inability to deal with enteric infections due to defective cellular and humoral immunity, common and unusual intestinal pathogens may establish a foothold and colonise the AIDS patients bowel causing intestinal infections/infestations. This may result in diarrhoea and lead to malabsorption and weight loss and also further loss of the all important T4 lymphocyte. Furthermore it has recently been demonstrated that AIDS enteropathy can exist in isolation of enteric pathogenic infection in the bowel. In fact, in its pure form AIDS enteropathy results from infection of the small bowel mucosal cells and colonic mucosal cells by the human immuno-deficiency virus (HIV) and can give rise to diarrhoea in the absence of secondary infections. Thus in addition to enteric luminal infections, the AIDS patient may be carrying HIV organisms within the enteric mucosal lining cells and in effect suffer from both AIDS enteropathy and enteric infection. Hence, this leads to further diarrhoea, weight loss and further reduction in the quality and length of the patients' life.

Patients positive for the HIV organism but who have not yet developed AIDS characterized by a secondary infection of unusual nature, are at risk of colonising their bowel with pathogens given time. As their total T4 lymphocyte level falls they become progressively more susceptible to development of a chronic infection/infestation thereby leading to malabsorption, weight loss and ultimately an accelerated terminal condition. Prevention of the acquisition of such enteric infection is, of course, helpful in prolonging the quality and length of life in patients infected with HIV. Apart from thorough cleansing and perhaps irradiation of food, it is not possible to prevent enteric infection because the food we eat carries numerous bacteria, viruses, fungi and other organisms.

It has been known for some time that immunisation of cows and harvesting of colostrum can be used to treat children with some enteric infections. We have recently demonstrated that not only patients with congenital hypogammaglobulinaemia but also with AIDS can be treated for the presence of enteric infections such as Cryptosporidium.

Object of the Invention

It is an object of the present invention to provide a method of treatment or prophylaxis of enteric infections/infestations in patients with a lowered immune response.

Disclosure of the Invention

The inventors recognised that immunocompromised patients and especially HIV infected individuals are susceptible to a wide range of infections/infestations including AIDS enteropathy per se, which are resistant to treatment by conventional techniques. The present invention therefore derives from the discovery that hyperimmune milk products obtained from animals challenged with a variety of immunogens, relating to pathogenic organisms associated with enteric infections/infestations in an immunocompromised host, are capable of preventing or treating such infections.

Thus in one form, the present invention provides a method for the curative and/or prophylactic treatment of enteric infections and infestations in immunologically compromised patients, said method comprising administering to said patient milk, a fraction thereof or a milk product, produced by a non-human milk producing animal or antibody product therefrom wherein the animal has been immunologically challenged with one or more immunogens relevant to the enteric infestation/infection.

Preferably said immunogens are selected from:

i) HIV virus/viruses, or antigenic product thereof

ii) enteric pathogens or antigenic product thereof collected from the patients with infections/infestations such as from patients stools, and/or

iii) microorganisms responsible for, and/or associated with, the enteric infection or infestation manifested by the patient, or antigens derived therefrom.

Microorganisms associated with enteric infections in patients with lowered immune response include one or more of the following:

a) Cryptosporidium enteritides,

b) Isoporo belli,

c) Giardia,
d) Cytomegalovirus,
e) Salmonella,
f) Shigelli,
g) Candida,
h) Rotavirus,
i) Blastocystis hominis,
j) Herpes virus simplex,
k) Entero-toxogenic E. coli,
l) Aeromonas,
m) Mycobacterium Avium intracellulare,
n) Yersinia entero-colitica,
o) Toxoplasma gondii,
p) Clostridium difficile,
q) Campylobacter jejuni/coli,
r) Entamoeba histolytica, and
s) HIV virus.

In a further form the invention provides a pharmaceutical composition useful in the treatment of enteric infections/infestations in patients having lowered immune response which comprises milk, an antibody-containing fraction thereof or a milk product derived from a non-human milk producing animal, preferably a mammal, wherein the animal has been immunologically challenged to give an immune response to an immunogen relevant to the infection/infestation.

Preferably the immunogen is selected from:

i) HIV virus/viruses, or

ii) one or more immunogens relevant to an enteric pathogen causative of, or associated with, enteric infections/infestations in said patients.

Preferably the immunogens are, or derived from, one or more of the following microorganisms:

a) Cryptosporidium enteritides,
b) Isoporo belli,
c) Giardia,
d) Cytomegalovirus,
e) Salmonella,
f) Shigelli,
g) Candida,
h) Rotavirus,

i) Blastocystis hominis,

j) Herpes virus simplex,

k) Entero-toxogenic E. coli,

l) Aeromonas,

m) Mycobacterium Avium intracellulare,

n) Yersinia entero-colitica,

o) Toxoplasma gondii,

p) Clostridium difficile,

q) Campylobacter jejuni/coli,

r) Entamoeba histolytica, and

s) HIV virus.

Preferably the animal is immunologically challenged with a number of the above selected immunogens to provide a "polyvalent" antibody response and hence to produce a milk which has a number of predetermined antibodies.

The milk producing animals are non-human and are preferably mammals selected from cows or goats. The animal is immunologically challenged with an immunogen described above. The immunisation may be carried out either subcutaneously, intra-muscularly, into the mammary tissue, or into the mammary ducts. In addition adjuvants may be used to enhance the antibody response. The animals immune response is monitored so that when a significant immune response to the selected immunogen or a marker amongst a variety of immunogens is observed, the milk, serum, or colostrum can be collected.

Colostrum, whole milk, or whey can then be used as a form of treatment for the enteric infestations and infections. Preferably the milk can further be treated to improve keeping qualities or shelf life and it can be flavoured or contained with other adjuvants.

In a preferred form for administration to a patient IgG antibodies are extracted from the milk by techniques well known in the art, freeze dried, and reconstituted before administration. Alternatively whole colostrum is freeze dried and reconstituted for use as a drink or a powder, or is made into a milk product such as ice-cream.

Best Mode and other Modes for Carrying out the Invention

Typically in the practice of the invention the milk is pasteurised at 62°C for thirty minutes and de-fatted by using a separator to leave less than 1% of the fat content within the product. A coarse (eg 1.0 micron) membrane can be used to filter out bacteria. The milk can be transferred to an ultra-filtration unit to remove lactose, water and smaller proteins (< 100,000) including lacto-albumin leaving behind the gammaglobulin as well

as small quantities of ash and minerals. The remaining sterile bovine milk antibody substance can then be placed in a freeze-drying unit to remove residual moisture and lyophilise the product. Once the freeze-drying cycle is completed the dried material can be placed into a colloid mill for pulverisation into fine powder. Antacid, flavouring agents and other excipients can be added to the powder as is required for the pharmacological product. The product can then be containerised into capsules, sachets, or bottles for reconstitution in the future. In this way a dried, light, high concentration of milk gammaglobulin can be delivered to the patient. The milk product as such can then be mixed further with vitamins and other nutrients required by the ill patient, and administered in the form of a drink such as a milkshake or in the form of ice-cream or other suitable product, depending on the age and clinical condition of the patient.

This product is useful in the treatment of enteric infestations and infections in patients having lowered immune response as well as being useful in the prevention of various infections.

Furthermore, specific anti-HIV antibody in the powdered product can be used by the patient to combat mucosal enteric cell infection with HIV. In this way, malabsorption will be reduced because milk-antibody is taken up into the enteric cell where it can come in contact with invading HIV.

In an alternative form, patients requiring such treatment can be treated with antibodies produced from a non-human animal immunologically challenged to give an immune response to an immunogen such as those selected from HIV viruses or bacteria or viruses related to enteric infestations in patients having lowered immune response. The preferred antibodies are antibodies to immunogens as defined above and these can be purified from the milk or serum of animals which are immunologically challenged with selected antigens. The antibodies, by methods known in the art, are prepared in the form of a pharmaceutical composition for oral, peritoneal or parenteral administration.

Administration of the above described pharmaceutical compositions will usually be on a regular basis over a relatively long period of time. As the patients have lowered immune response, the continued administration of the compositions will substantially decrease the enteric pathogens at which the composition is directed. However once administration is stopped, there is the possibility that the pathogens will reinfest the gastrointestinal tract of the patient and the symptoms will reappear.

Therefore, continued and prolonged administration is desirable, for example in the form of a drink three times daily. In one preferred form of the invention, the milk or milk product or antibody preparation is administered to the patient after or concurrently with an agent suppressing gastric acid to reduce protein denaturation within the stomach. Such agents include ranitindine, cimetidine, famotidine, and omeprazole.

It has been found that the antibodies administered according to the method of the invention remain stable through passage through the stomach and reach the small bowel and in fact pass into the stool showing full activity.

Alternative sources of antibodies can be obtained from specific monoclonal production utilising routine myeloma cell lines. Monoclonal antibody can be ultrafiltered and purified with coarse membrane to remove bacteria, fluid, and other impurities. In a similar way it can be lyophilised and pulverised to a fine powder. Antibody can be again alternatively produced by the introduction of appropriate genetic material into bacteria ordering them to elaborate a particular gammaglobulin required to treat an infection in the lumen or an HIV infection overall and extracting and purifying the gammaglobulin obtained.

The invention will now be further described by reference to the following non-limiting example.

Example

A forty year old male with AIDS with a previous twelve month history of diarrhoea and weight loss due to Cryptosporidium not responding to treatment with Spiramycin was treated with 500 ml of immune bovine colostrum daily via naso-gastric tube. After twenty-one days of therapy the patient totally recovered from his diarrhoea and remained free of diarrhoea thereafter. Even though the infection remained sub-clinical, the patient was well. Hence, a clinical improvement could be obtained by the use of antibody obtained from bovine milk. The presence of Cryptosporidium in the biliary system allows the therapy not to be totally curative in this case, but clinically significant in alleviating symptoms. It is concluded that the immune bovine colostrum cleared the patient's parasite from the proximal or even the entire small intestine. The patient's disease did not recur and he died three and a half months later from other AIDS related complications.

The claims defining the invention are as follows:

1. A method for the curative and/or prophylactic treatment of enteric infections/infestations in patients suffering from conditions wherein a lowered immune response is manifested, said method comprising administering to said patient milk, a fraction thereof or milk product produced by a non-human, milk producing animal or antibody product derived therefrom, wherein the animal has been immunologically challenged, to give an immune response, with one or more immunogens relevant to the enteric infection/infestation.

2. The method of Claim 1 wherein said animal is a cow or goat.

3. The method of Claim 1 or 2 wherein said immunogen is selected from:

i) HIV virus/viruses or antigenic fraction thereof,

ii) enteric pathogens or antigenic fractions derived therefrom collected from patients with the infection/infestation, and/or

iii) microorganisms or antigenic product thereof, responsible for, and/or associated with, the enteric infection/infestation manifested by the patient.

4. The method of Claim 1 wherein said immunogen is selected from the following microorganisms:

a) Cryptosporidium enteritides,
b) Isoporo belli,
c) Giardia,
d) Cytomegalovirus,
e) Salmonella,
f) Shigelli,
g) Candida,
h) Rotavirus,
i) Blastocystis hominis,
j) Herpes virus simplex,
k) Entero-toxogenic E. coli,
l) Aeromonas,
m) Mycobacterium Avium intracellulare,
n) Yersinia entero-colitica,
o) Toxoplasma gondii,
p) Clostridium difficile,

q) Campylobacter jejuni/coli,

r) Entamoeba histolytica, and

s) HIV virus.

5. The method of Claim 3 wherein said immunogen is selected from HIV virus/viruses or antigenic product thereof together with one or more other immunogens and said patients condition is AIDS or HIV related.

6. The method of Claim 5 wherein the enteric cells of the patient have been infected with at least one strain of HIV.

7. A pharmaceutical composition useful in the treatment or prophylaxis of enteric infections/infestations in patients with conditions wherein a lowered immune response is manifested, which composition comprises milk, an antibody-containing fraction thereof or milk product derived from a non-human, milk producing animal wherein the animal has been immunoiogically challenged, to give an immune response, to one or more immunogens relevant to said enteric infection/infestation.

8. The composition of Claim 7 wherein said one or more immunogens is selected from:

i) HIV virus/viruses or antigenic product thereof,

ii) immunogens relevant to an enteric pathogen causative of, or associated with, enteric infections/infestations in said patients.

9. The composition of Claim 8 wherein said immunogens are, or derived from, one or more microorganisms selected from:

a) Cryptosporidium enteritides,

b) Isoporo belli,

c) Giardia,

d) Cytomegalovirus,

e) Salmonella,

f) Shigelli,

g) Candida,

h) Rotavirus,

i) Blastocystis hominis,

j) Herpes virus simplex,

k) Entero-toxogenic E. coli,

l) Aeromonas,

m) Mycobacterium Avium Intracellulare,

n) Yersinia entero-colitica,

o) Toxoplasma gondii,

p) Clostridium difficile,

q) Campylobacter jejuni/coli,

r) Entamoeba histolytica, and

s) HIV virus.

10. The composition of any one of Claims 7, 8 or 9 wherein said animal is a cow or goat.

11. The composition of any one of Claims 7 to 9 wherein one of said immunogens is HIV virus or antigenic product thereof.

12. The composition of any one of Claims 7 to 11 wherein said composition is a freeze dried milk product suitable for reconstitution.

13. The composition of any one of Claims 7 to 11 wherein said composition is a freeze dried antibody extract.

DATED this FOURTH day of AUGUST 1989

Thomas Julius Borody

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SPRUSON & FERGUSON